Neuroradiology (2008) 50:1035–1039
DOI 10.1007/s00234-008-0455-x

INTERVENTIONAL NEURORADIOLOGY

Disruption of the blood–brain barrier by intra-arterial administration of papaverine: a technical note

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Received: 8 April 2008 / Accepted: 27 August 2008 / Published online: 13 September 2008

Abstract
Introduction Various endovascular techniques can be used to treat cerebral vasospasm after aneurysmal subarachnoid haemorrhage (SAH) including intra-arterial administration of vasodilator drugs such as papaverine or nicardipine and balloon dilatation of the affected vessel segment. Papaverine is known to have side effects, and we report a possible new one.
Materials and methods After the treatment of cerebral vasospasm in a SAH patient by intra-arterial administration of papaverine into the left posterior cerebral artery, severe mesencephalic extravasation of blood and contrast media was detected.
Results After reviewing the literature, the authors conclude that interruption of the blood–brain barrier by papaverine most likely combined with a secondary hyperperfusion phenomena, and perhaps a direct toxic effect on brain tissue was the mechanism of this major complication.
Conclusion In treating vasospasm in areas with a high density of perforating arteries, especially in the posterior circulation, papaverine should be used cautiously because a safe regimen has yet to be established. In this situation, alternative agents such as calcium channel blockers could be considered, but evidence-based data are still missing.

Keywords Intra-arterial administration of papaverine · Vasospasm · Subarachnoid hemorrhage · Complication of treatment

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Introduction

Cerebral vasospasm remains a major problem in the subacute treatment of subarachnoid haemorrhage (SAH). Angiographically detectable in about 70% of patients, it leads to delayed neurological deficits in 20% to 30%, with 7% of patients dying [1]. Various endovascular techniques were developed to treat vasospasm including intra-arterial administration of papaverine (IAP), which was introduced in 1992 [2–4]. Papaverine leads to an improvement of cerebral blood flow (CBF) by dilating the proximal, intermediate, and distal cerebral arteries [5–8]. As a result, oxygen supply is increased, preventing further lactate brain acidosis and facilitating recovery [9, 10].

Angiographic improvement is achieved in up to 96% and clinical improvement in 33% to 80% [5, 10–12]. Here, we describe a new complication of IAP.

Case presentation

A ruptured anterior communicating artery aneurysm was clipped in a 67-year-old woman suffering SAH (Fig. 1a,b). Seven days later, vasospasm was suspected on transcranial duplex ultrasound. A computed tomography (CT) perfusion scan showed changes typical of vasospasm in the left posterior cerebral artery (PCA) territory (Fig. 1c,d [13–15]), and digital subtraction angiogram confirmed vasospasm in

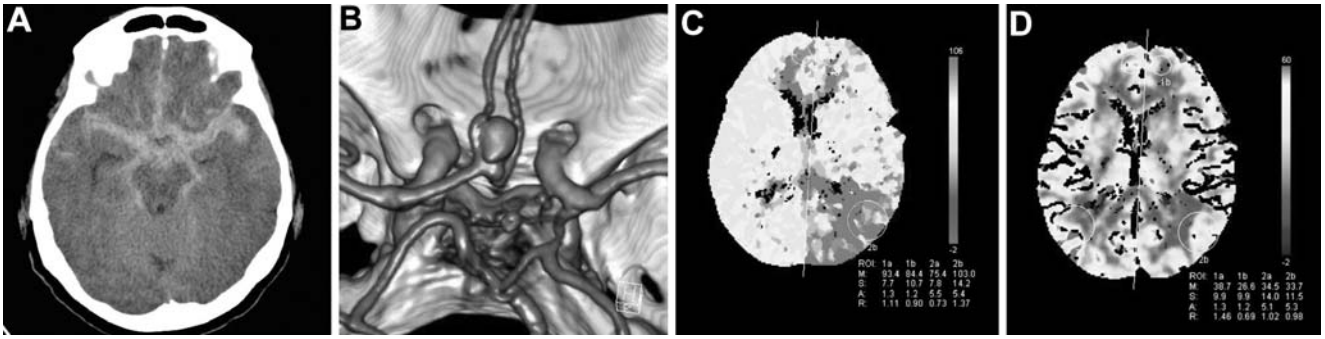

Fig. 1 **a** CT on admission, showing excessive SAH (Fisher grade 3, Hunt & Hess grade 5). **b** Aneurysm of the anterior communicating artery detected in computed tomography angiography. **c**, **d** CT perfusion: Prolonged time to peak (**c**) and normal cerebral blood volume (**d**) in the left PCA territory, while CBF was slightly decreased without new infarctions in cranial computed tomography (data not shown)

the left P1 segment (Fig. 2a,b). IAP was indicated [16], and a FastTracker 10 catheter was easily placed at the origin of the left PCA and an initial infusion of 150 mg papaverine (diluted to 0.3%) made over 25 min without improvement in the vessel diameter (Fig. 2c). Therefore, another 150 mg papaverine was administered, and the vasospasm relieved (Fig. 2d).

Following the infusion, the left pupil was found to have dilatated, though intracranial pressure (ICP) remained normal. An immediate brain CT showed a new lesion in the left mesencephalon without significant mass effect or crossing of the midline (Fig. 3).

The patient was referred to the intensive care unit. As vasospasm worsened, hypothermia and barbiturate coma were initiated [17], but no further endovascular interventions were undertaken. Follow-up CT scans showed progressive infarctions, and resolution of the mesencephalic hyperdensity resolved. The patient died on day 25.

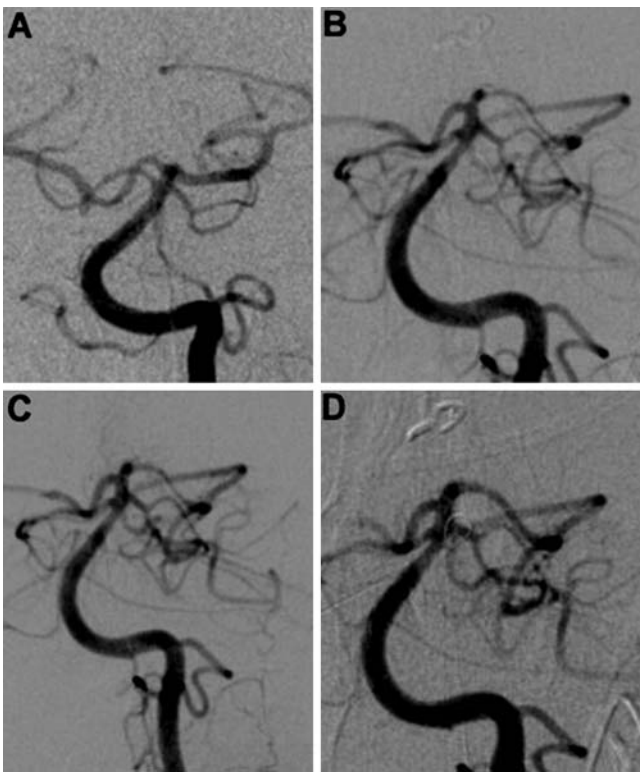

Fig. 2 **a** Initial angiogram showing normal vessel diameters. **b** Vasospasm of the left P1 segment before IAP. **c** Control after administration of 150 mg of papaverine showing no relevant change in the vessel caliber. **d** Final angiographic control after administration of a total of 300 mg showing no hints for a vessel rupture

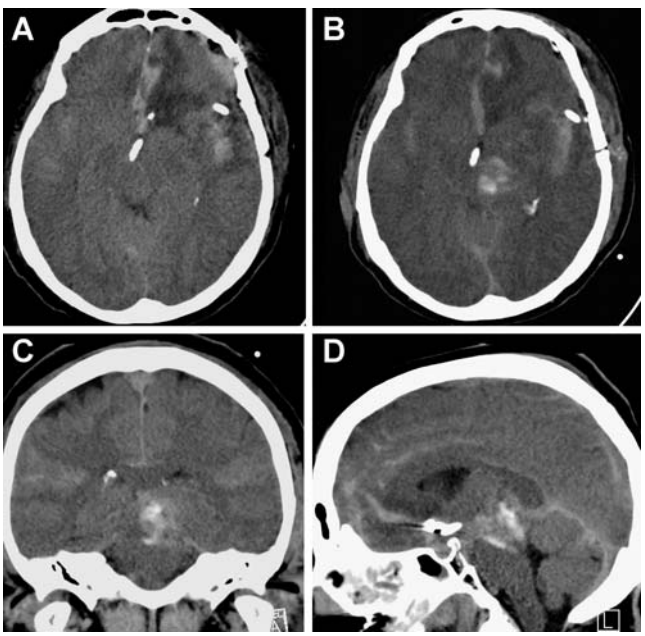

Fig. 3 Immediately after IAP, a new hyperdense lesion is noted in the left mesencephalon without crossing of the midline (**b**, **c**, **d**) when compared to the CT before the procedure (**a**). Note the absence of a significant mass effect as one would expect in the case of hemorrhage. Furthermore, no vessel rupture or extravasation of contrast dye was noted during the procedure. The Hounsfield units (55 to 110) of more than 100 suggest that also part of the contrast dye contributes to the extravasation

Discussion

Papaverine acts directly on vascular smooth muscle cells by inhibiting cyclic adenosine monophosphate and cyclic guanosine 3,5 monophosphate leading to vasodilatation [18]. We have routinely performed IAP, with good results, since 1993 [4, 9, 16, 17, 19]. The incident reported here with a new intraparenchymal hyperdensity without mass effect has not been observed before.

Three mechanisms may play a role. First, evidence from animal studies suggests that infusion of papaverine may lead to a disruption of the blood–brain barrier (BBB) with extravasation of blood and radiographic contrast agents [20]. Another group noted that, in higher concentrations, papaverine may damage luminal endothelial and smooth muscle cells because of its high acidity [21]. Besides, high concentrations of the drug may lead to its precipitation and subsequent microembolization [22–24]. Second, because IAP locally increases CBF through vasodilatation [7, 25], hyperperfusion after treatment may facilitate extravasation [12], especially in the presence of a damaged BBB. Third, a direct neurotoxic effect of papaverine seems possible. Smith et al. detected changes in the gray matter and in the neurological status of patients after treatment with IAP. Based on their imaging data and a pathological examination, they suggest that IAP leads to a blockade of mitochondrial respiration and inhibition of the Krebs cycle [26]. Considering the almost immediate effect in our case, this mechanism does not seem to have played an important role but may have contributed to the devastating outcome.

Although dilutions of 0.6% papaverine have been administered in humans without complications [27], this concentration might easily be exceeded locally in the presence of vasospasm. A distal spastic vessel segment may reduce the physiological dilution of papaverine, and an accumulation of the drug in proximal perforators may cause damage of the vessel wall [21].

Although we cannot exclude preexisting ischemia in the affected area making the tissue more vulnerable, the absence of clinical symptoms or hypodensities on CT before treatment makes this unlikely (Fig. 3a), and the findings on CT perfusion were not typical for irreversible infarction [28]. In circumstances similar to our patient, McAuliffe et al. reported a patient who died due to a hemorrhage in the basal ganglia immediately after IAP in this territory. The authors excluded vessel rupture as the cause [29].

The dose and infusion rate of papaverine remain unsolved, and published guidelines are lacking. In the literature, 150 to 300 mg papaverine administered per vessel segment seems to be a generally accepted dose [1, 3, 7, 9–11, 16, 22, 30–35]. However, reported doses vary widely from a few milligrams [2, 5] to more than 400 mg [26, 27, 32, 35]. For the posterior circulation, only few cases have been published [9, 27, 32]. Furthermore, recommended infusion rates vary substantially between 15 to 60 min for 300 mg [3, 6, 7, 22, 26, 30–34]. In our case, either the dose (300 mg) or the rate (50 min) or both seem to have been inappropriate. Therefore, we recommend using less than 300 mg per segment in the posterior circulation at even slower infusion rates than usual.

There are alternative drugs for the endovascular treatment of vasospasm. Most of them are calcium channel antagonists, e.g., nimodipine or nicardipine. But there are only small series reported in the literature with success rates ranging from 43% to 100% and from 29% to 89% as measured by increase in vessel diameter and neurological improvement, respectively. Adverse effects, such as circulatory events or, infrequently, ICP increase, were described in 0% to 33% of patients [1, 36–38]. Compared to papaverine, a direct neuroprotective effect of nimodipine has been postulated [1], while the problem of a transient treatment effect remains [39].

Conclusion

We assume that our case was the result of a combination of factors in which pathological hemodynamics due to vasospasm caused an unexpected high concentration of papaverine in perforator vessels, leading to BBB disruption with extravasation of blood and contrast media, possibly facilitated by secondary hyperperfusion. Therefore, we suggest a very cautious use of the drug especially in areas with numerous perforators proximal to a vasospastic segment. Safe infusion rates and dosage still need to be established. On the other hand, further studies need to prove the potential advantage of alternative drugs such as calcium channel antagonists.

Conflict of interest statement We declare that we have no conflict of interest.

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